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Chronic Relapsing Thrombotic Thrombocytopenic Purpura and Antiphospholipid Antibodies: A Report of Two Cases

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We report on 2 cases of chronic relapsing thrombotic thrombocytopenic purpura, in which anti-phospholipid antibodies were also found. The first patient was felt to have the anti-phospholipid antibody syndrome, while the second patient had anti-phospholipid antibodies without clinical manifestations of the anti-phospholipid antibody syndrome. We discuss chronic relapsing thrombotic thrombocytopenic purpura and the anti-phospholipid antibody syndrome. Furthermore, we introduce the possibility of an association between chronic relapsing thrombotic thrombocytopenic purpura and the presence of anti-phospholipid antibodies. Am. J. Hematol. 54:155–159, 1997 © 1997 Wiley-Liss, Inc.

Key words: thrombotic thrombocytopenic purpura; anti-phospholipid antibodies; anti-phospholipid antibody syndrome

INTRODUCTION

The anti-phospholipid antibody syndrome (APS) has been defined as the presence of anti-phospholipid antibodies or lupus anticoagulant in association with certain clinical events, including recurrent arterial or venous thromboses and recurrent fetal loss [1,2], and it has been treated successfully with prolonged anticoagulation [3,4]. Thrombotic thrombocytopenic purpura (TTP) is a severe, multisystemic disorder characterized by microangiopathic hemolytic anemia, thrombocytopenia, neurologic manifestations, and often fever and renal dysfunction [5], which has been effectively treated with plasma transfusion and/or plasmapheresis [6]. The majority of patients experience only a single episode of TTP, but relapses do occur. Occasionally, chronic relapsing TTP is observed. This entity can be defined as frequent episodes of TTP varying in severity at regular intervals [7]. The interval between TTP relapses is usually a few weeks. An association between TTP and APS or anti-phospholipid antibodies has not been clearly established. We describe a patient with both chronic relapsing TTP and APS. Secondly, we describe a patient with relapsing TTP and strong positive anti-phospholipid antibodies.

CASE REPORTS

Patient 1

A 26-year-old, previously healthy white female was admitted to a local hospital on October 8, 1993, with acute onset of transient dysarthria and bilateral upper extremity clumsiness and numbness. Her physical examination was significant only for a systolic murmur. Laboratory studies revealed a hematocrit of 25% with numerous schistocytes on the peripheral blood smear, platelet count of 49,000/μl, lactate dehydrogenase (LDH) of 1,090 U/l (normal range, 80–235 U/l), normal prothrombin time (PT) and partial thromboplastin time (PTT), and serum creatinine of 1.5 mg/dl. Direct Coombs' test and an antinuclear antibody test were negative. A CT scan of the head was unremarkable. A transesophageal echocardiogram revealed a solitary 4×6 mm pedunculated echogenic structure on the left atrial surface of the posterior mitral valve leaflet. Cultures of blood were repeatedly negative. An atrial myxoma was suspected, and the patient underwent surgical excision of two masses from the posterior leaflet of the mitral valve and one from the anterior leaflet. On pathologic review these were found to be thrombi with ossification and calcification. The patient did well postoperatively and was discharged with a hematocrit of 25% and a platelet count of 98,000/μl.

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Two weeks later, she was asymptomatic without any therapy; however, her platelet count had decreased to 36,000/μl. Her hematocrit was 29%, LDH 832 U/l, and serum creatinine 1.6 mg/dl. Serum haptoglobin was low at 2 mg/dl. Numerous schistocytes were present on the peripheral blood smear. The patient was administered prednisone, 20 mg daily, by her local physician. Five days later, she was admitted to Shands Hospital (Gainesville, Florida) after experiencing transient numbness of her forearm, hand, and occipital scalp. She was afebrile. Neurologic examination revealed normal motor and sensory function. Hematocrit was 27.8%, and platelet count 46,000/μl. An uncorrected reticulocyte count was 10%. PT, PTT, and fibrinogen level were normal. Tests for lupus anticoagulant, VDRL and antinuclear, and native DNA and HIV antibodies were negative. Anti-phospholipid and anti-cardiolipin antibody titers were measured by enzyme-linked immunosorbent assay (ELISA), devised by Gharavi et al. [8]. These were significant for a strong positive antiphosphotidylinositol IgM at a mean +7.8 standard deviations (SD) (a negative result is defined as relative OD values <2 SD above the mean, weak positive is 2–4 SD above the mean, positive is 4–6 SD above the mean, and strong positive is >6 SD above the mean).

A transthoracic echocardiogram revealed a probable vegetation involving the mitral valve. Blood cultures for bacteria and fungus were negative. Anticoagulation with intravenous heparin was initiated. After 48 hr of heparin therapy, the patient developed acute onset of left occipital headache, right homonymous hemianopsia, and expressive aphasia. She was not therapeutically anticoagulated on heparin, however, with a PTT of 40 sec (normal, 19–33 sec). A repeat CT scan of the brain revealed a large infarction involving the left posterior parietal and occipital lobes. A nuclear perfusion study of the kidneys, liver, and spleen revealed multiple infarctions of the kidneys and spleen consistent with thromboembolic disease. Intravenous heparin was continued, and PTT was maintained at >60 sec. She had no further neurologic symptoms until hospital day 7, when she was noted to be anxious, combative, and disoriented. She had persistent schistocytes, and her platelet count was 35,000/μl. The diagnosis of TTP was considered, intravenous methylprednisolone 50 mg every 6 hr was administered, and plasmapheresis was performed using 3 l fresh-frozen plasma (FFP) as replacement fluid. On the following day her mental status had returned to baseline, her platelet count had increased to 60,000/μl, and LDH had decreased to 328 U/l. She had daily plasmapheresis for 5 days with complete normalization of her platelet count, LDH, and creatinine. Plasmapheresis was then tapered to every-other-day treatments and discontinued after a total of eight cycles. She was discharged on warfarin and prednisone with a hematocrit of 35.8%, platelet count of 364,000/μl, and INR in the therapeutic range. Unfortunately, evidence of a microangiopathic hemolytic anemia with significant progressive thrombocytopenia persisted. She was treated with periodic infusions of plasma, with prompt impressive increases in platelet count, but the response was of limited duration (Fig. 1). Prednisone was discontinued; however, the patient continued on warfarin, maintaining INR in the 2.0–3.5 range. In April 1994, 5 months after her initial presentation, she continued to have a positive antiphosphotidylinositol IgM (mean +4.32 SD), and had developed strongly positive IgM and weakly positive IgG antiphosphotidylserine antibodies. From August 1994 to the present time, two units of FFP administered every 2 weeks has been required to maintain a normal platelet count. In November 1995, an interval of 3 weeks between FFP infusions occurred and the platelet count dropped to 51,000/μl. Clinically, the patient has developed arthralgias; however, there have been no new thromboembolic events or development of focal neurologic deficits.

Patient 2

A 19-year-old white female presented to a local hospital on December 15, 1993, with bruising and menorrhagia. Physical exam was significant for temperature of 37.8°C and ecchymoses of the forearms. Laboratory studies demonstrated a hematocrit of 31%, platelet count of 7,000/μl, white blood cell count of 10,400/μl, corrected reticulocyte count of 1.8%, serum creatinine of 0.9 mg/dl, negative ANA screen, and negative direct Coombs' test. The peripheral blood smear revealed rare schistocytes. A bone-marrow aspirate demonstrated a normal number of megakaryocytes. She was treated with intravenous gamma globulin and prednisone for suspected idiopathic thrombocytopenic purpura. However, after 48 hr of treatment, hematocrit had decreased to 23.4% and platelets to 4,000/μl. She was transferred to Shands Hospital on December 18, 1993. Her physical exam remained unchanged. Hematocrit was 16%, platelets 4,500/μl, serum creatinine 1.3 mg/dl, and LDH 868 U/l. Peripheral blood smear now revealed numerous schistocytes. There was no clinical or laboratory evidence of disseminated intravascular coagulation. Plasmapheresis with approximately 3 l of FFP as replacement fluid was immediately initiated and continued daily. After 4 days the platelet count increased to 52,000/μl; however, the following day it dropped to 13,000/μl. She was then treated with twice-daily plasmapheresis, one dose of vincristine 1 mg and prednisone 60 mg daily. After an additional 4 days the platelet count had increased to 400,000/μl and the hemolytic anemia had resolved. On March 8, 1994, she was readmitted to Shands Hospital with relapsed TTP, manifested by thrombocytopenia and microangiopathic hemolytic anemia, after an upper respiratory infection. She was treated with twice-daily plasmapheresis, vincristine, and prednisone. She was discharged on March 31, 1994 and

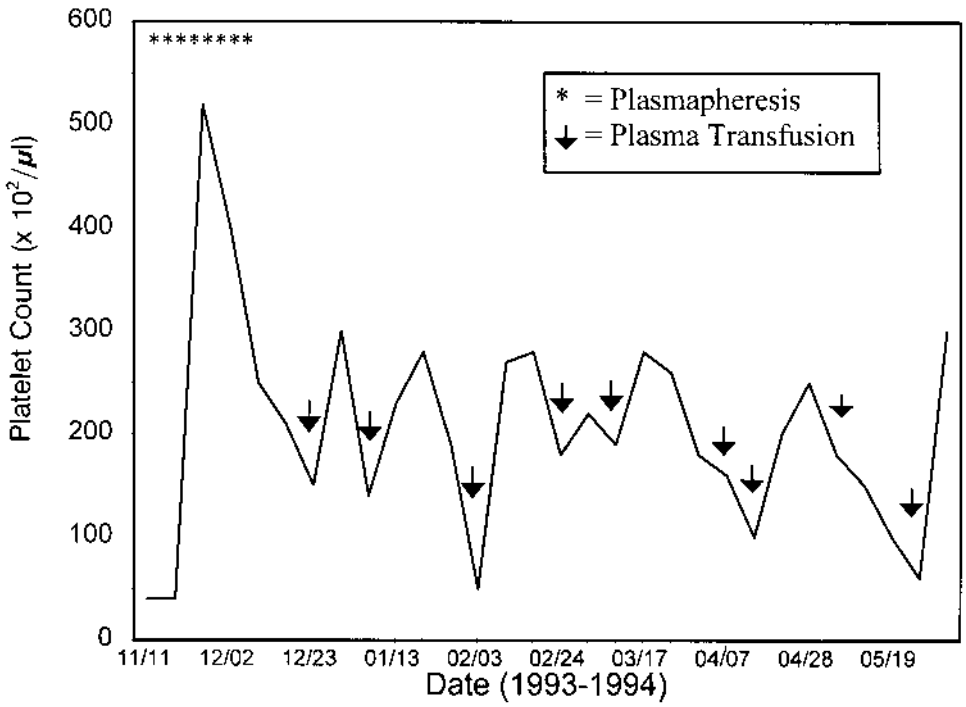

Fig. 1. Platelet count response to plasma transfusion. Periodic transfusions of fresh-frozen plasma (FFP) resulted in temporary increases in the platelet count of patient 1.

received twice-weekly plasma infusions for approximately 2 months. On November 1, 1994, she presented with clinical and laboratory manifestations of relapsed TTP. After successful treatment with plasmapheresis she was maintained on plasma infusions for several weeks. Subsequent relapses of TTP occurred in March, September, and October of 1995. Since October 1995 she has been maintained on periodic plasma infusions. Her platelet count has remained >200,000/μl and she has had no symptoms referable to TTP. Anti-phospholipid and anti-cardiolipin antibody testing, and lupus anticoagulant testing were performed during a TTP relapse in November 1994. A weakly positive antiphosphotidylserine IgM (mean + 2.67 SD) antibody titer was present. Anti-cardiolipin antibodies were negative, and lupus anticoagulant was negative, although heparin contamination of the plasma sample precluded reliable results. Antiphospholipid and anti-cardiolipin antibody testing was repeated in October 1995 and revealed a positive antiphosphotidylserine IgM (mean + 4.86 SD) and strongly positive antiphosphotidylinositol IgM (mean + 6.09 SD).

DISCUSSION

Our first patient was found to have evidence of both TTP and APS. Nesher et al. [9] reported their experience of 4 patients with thrombotic microangiopathic hemolytic anemia and systemic lupus erythematosus (SLE), and described 24 similar patients from a literature review. They estimated that thrombotic microangiopathic hemolytic anemia occurs in at least 2–3% of SLE patients. In their review of these 28 patients, 89% presented as TTP and 11% presented as hemolytic uremic syndrome (HUS). The presence of anti-phospholipid antibodies was looked for in 8 cases, and elevated titers were identified in 5 individuals. There have been two previous case reports on apparently non-SLE-associated APS with TTP [10,11]. In one case, a rise in the anti-cardiolipin antibody level occurred at time of TTP onset [10]. Two reports have noted an association between circulating lupus anticoagulant or anti-cardiolipin antibodies and postpartum HUS [12,13]. In one of these reports, plasma exchange resulted in a decline in anti-cardiolipin antibody titer and improvement in the patient's clinical condition [12].

Particularly striking is the finding of fibrin deposition on the mitral valve apparatus of patient 1. In addition, there was evidence of multiple infarcts involving the spleen, kidneys, and, most significantly, the brain, consistent with emboli. In this patient, the microangiopathic hemolytic anemia and significant thrombocytopenia would appear to be a manifestation of TTP, as evidenced by the response in the blood counts to plasmapheresis. The etiology of her neurologic findings, i.e., TTP or APS, is more difficult to discern. The characteristic spectrum of neurologic manifestations of TTP includes headache, confusion, altered sensorium, paresis, aphasia, visual

changes, seizures, paresthesias, and coma [5]. However, these are usually transient in nature and often fluctuating. Generally, these fluctuating neurologic deficits have been felt to be secondary to microthrombotic and/or microhemorrhagic events [14], but extensive infarction of the brain, as in our case, would be unusual [15,16]. More recently, however, attention has been focused on the long-term neurologic sequelae in patients with TTP. In a review of 39 patients with TTP, 5 developed permanent neurologic deficits, with brain infarcts noted by CT scan in 2 cases [17]. In another study, Kay et al. [18] found that 10 of 20 patients with TTP had abnormal CT scans of the brain, including acute infarction in 6 and hemorrhage in 3 cases. In neither study were anti-phospholipid antibodies measured. The cerebral vasculature has been found to be a very common site of arterial thrombosis in patients with APS [1,3,4,19].

Cardiac lesions, and in particular valvular lesions, have been associated with anti-phospholipid antibodies in SLE and non-SLE patients. Galve et al. [20] found that 10 of 28 patients with primary APS had cardiac valvular involvement. Valvular involvement in this study was defined by valvular thickening and regurgitation. In a study by Barbut et al. [21], 26 of 87 patients with aortic or mitral regurgitation or both had positive IgG anti-cardiolipin antibodies compared with 0 of 24 normal subjects. Focal cerebral ischemic events occurred more often in those patients with positive anti-cardiolipin antibody titers and valvular lesions compared to those with valvular lesions without elevated anti-cardiolipin antibody titers. Vegetations of the mitral valve were identified in 8 of 50 patients with SLE, along with an associated elevated anti-phospholipid antibody titer in a study reported by Khamashta et al. [22]. Large intracardiac thrombi have been noted to mimic atrial myxomas in some patients [4]. In an autopsy study of patients with TTP, Ridolfi et al. [16] noted nonbacterial endocarditis involving the mitral valve in 2 of 17 patients. This report appeared prior to the availability of sensitive assays for anti-phospholipid and anti-cardiolipin antibodies; however, lupus anticoagulant status was not reported.

Patient 2 did not have APS; however, she did have strongly positive antiphosphotidylinositol IgM and positive antiphosphotidylserine IgM antibody titers on most recent testing. The first time she was tested for antiphospholipid antibodies, there was only a weakly positive antiphosphotidylserine IgM. This initial testing was performed after several days of plasmapheresis, and may have been affected by this manipulation.

Only rarely is the chronic relapsing variant of TTP observed. Both patients presented in this report have criteria for chronic relapsing TTP, i.e., frequent episodes of TTP occurring at regular intervals of a few weeks [7]. Moake et al. [23] reported the presence of unusually large von Willebrand factor (vWF) multimers in the plasma of patients with chronic relapsing TTP. Levels were higher during periods of remission. Their hypothesis was that an unidentified cofactor was present during TTP relapses which promoted interaction between platelets and the unusually large vWF multimers. Our first patient was found to have unusually large vWF multimers in her plasma during TTP remission (Dr. Joel Moake, personal communication). Plasma from our second patient has not been analyzed for the presence of unusually large vWF multimers. It remains uncertain whether the susceptibility to chronic relapsing TTP is congenital, acquired, or both [23–25].

The treatment of chronic relapsing TTP is often frustrating. Infusion of FFP can be beneficial in preventing as well as treating TTP relapses [26]. According to Moake et al. [23], infusion of FFP may provide the depolymerase activity needed to process the unusually large vWF multimers into the usual smaller forms, or to provide plasma proteins needed to eliminate the inciting cofactor. Cryosupernatant has also been shown to be effective in the prevention and treatment of chronic relapsing TTP [27]. Several reports have also noted clinical improvement with the immunosuppressive agents prednisone, azathioprine, vincristine, and cyclophosphamide [26,28,29].

CONCLUSIONS

We observed elevated anti-phospholipid antibodies titers in 2 patients with chronic relapsing TTP. These antibodies may play a role in the pathogenesis of TTP by initiating endothelial damage, which could facilitiate thrombus formation in the microcirculation. It has been demonstrated that monoclonal antibodies with lupus anticoagulant activity induce apoptosis of umbilical vein endothelial cells [30]. Laurence et al. [31] recently reported that plasma from patients with acute TTP could induce apoptosis in cultured endothelial cells of microvascular origin, but not from large vessels. The identification of anti-phospholipid antibodies in a significant number of patients with TTP, especially the chronic relapsing variant, would provide an impetus to further investigate the relationship of endothelial cell apoptosis and the development of thrombotic microangiopathies.

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